DETAILED ACTION

Applicant's claim amendments filed on 12/21/2009 have been entered.

Claims 2-3, 8-10, 16, 17, 23, 27, and 31 are cancelled. Claims 1, 18-22, 24-26, and 28 are amended. Claims 35-39 are newly added. Claims 1, 4-7, 11-15, 18-22, 24-26, 28-30, 32-39 are pending and currently under examination.

This application 10/690,199 filed on Oct. 21, 2003 claims benefit of provisional application 60/420,425 filed on Oct. 22, 2002. The publication number of this application 10/690,199 is US 2004/0223949 A1, published on Nov. 11, 2004.

Claim Objections

1. Claim 36 and 37 is objected to because of the following informalities: Newly added claim 36 recites "the peptides YLEPGPVTV and IMDQVPFSV" and newly added claim 37 recites "between about 1.5 and 17 months after step (a)". SEQ ID numbers are required for the peptide sequences recited in claim 36, as claims 24, 25, and 26 are written. With regard to claim 37, Applicant is advised to clarify on the record whether "1,5" is an artifact resulting from scanning process and is meant to be "15" or "1,5" is in fact intended to mean "1.5" as it appears. Appropriate correction is required.

Claim Rejection – 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Previous rejection of claims 18-22 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the claims have been amended to recite "step b)" in line 1 of each of these claims and Applicant's arguments have been fully considered and found persuasive.

With regard to whether the tem "at least 10 MU/m^2/day" referring to daily administration, Applicant states that the term "at least 10 MU/m^2/day" is meant to indicate, for instance, that step (b) begins on day 1 with administration of at least 10 MU/m^2 IFNα2b through the course of that day, which may then be repeated at a particular interval, such as every day (e.g., daily), a certain number of times per week (e.g., three times per week), or the like, as desired. Thus, term "/day" refers to the amount that is administered during the course of one day (e.g. "per day"). Applicant argues that the meaning of this term would be understood by one of skill in the art.

3. Previous rejection of claims 11 and 12 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the claims have been amended to recite "step b)" in line 1 of each of these claims and Applicant's arguments filed on 12/21/2009 have been fully considered and found persuasive.

For the clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 4-5 of the office action mailed on 06/19/2009 is reiterated below.

Claim 11 recites "wherein the melanoma-associated tumor antigen is selected from the group consisting of gpl00, MART-I/Melan A, gp75/TRP-I, tyrosinase, NY-ESO-I, melanoma proteoglycan, a MAGE antigen, a BAGE antigen, a GAGE antigen, a fragments thereof, and a derivative thereof".

Claim 12 recites "wherein the melanoma-associated tumor antigen is selected from the group consisting of gpl00, MAGE-I, MAGE-2, MAGE-3, MAGE-4, MAGE-6, MAGEI2, MAGE-51, GAGE-I, and GAGE-2".

It is noted that the specification and the status of art support that a NY-ESO-1 antigen, a MAGE antigen, a BAGE antigen, and a GAGE antigen, recited in amended claim 11 and 12 are tumor antigens. However, the specification and the status of art do not support that a NY-ESO-1 antigen, a BAGE antigen, and a GAGE antigen, recited in amended claim 11 and 12 are melanoma-associated tumor antigens. In the art, a NY-ESO-1 antigen, a BAGE antigen, and a GAGE antigen are not considered as tumor-specific antigen since they are expressed in various normal tissues including testis and placenta (See Table 1, page 302, Vujanovic et al., *J Cell Biochem.* 102(2):301-10, 2007). There is no evidence in the specification or in the art supports that a NY-ESO-1 antigen, a BAGE antigen, and a GAGE antigen are "melanoma-associated antigen" as recited in claims 11 and 12. This issue has been discussed on page 10 of the office action mailed on 01/07/2008, as well as on pages 8-9 of the office action mailed on 10/28/2008, see the teachings by Vujanovic et al., 2007 (See Table 1, page 302, Vujanovic et al., Melanoma cancer vaccines and anti-tumor T cell responses. *J Cell Biochem.* 102(2):301-10, 2007) and Flad et al., 1998 (Flad et al., Direct identification of major histocompatibility complex class I- bound tumor-associated peptide antigens of a renal carcinoma cell line by a novel mass spectrometric method, Cancer Res. 58(24):5803-11., 1998)

Applicant's arguments

Applicant argues that in describing NY-ESO-1 at paragraph [0018], Applicants' specification points to WO 98/14464 (pub. April 9, 1998, which corresponds to U.S. Pat. No. 5,804,381). As shown therein, NY-ESO-1 is expressed in melanoma tumor tissues (e.g., Table 4). Thus, both the specification and the art support the position that NY- FSO-1 is a melanoma-associated antigen.

In describing BAGE at paragraph [0018], Applicants' specification points to Boel et al. (Immunity, vol. 2, pp. 167-:175, pub. Feb. 1995; attached). As shown, therein, expression of BAGE was observed in melanoma tumor tissues (e.g., p. 169, first column, second full paragraph, BAGE "is expressed mainly in melanomas (22%)", see also Table 2). Thus, both the specification and the art support the position that, BAGE is a melanoma-associated antigen.

In describing GAGE at paragraph [0018], Applicants' specification points to Van den Eynde, et al. (J. Exp. Med., I82:689-698 (1995), attached) and U.S. Pat. No. 6,013,765. As shown therein, expression of GAGE was observed in melanoma tumor tissues (e.g., Van den Eynde, p. 689, Abstract, GAGE is "expressed in a significant proportion of melanomas (24%)"), Thus, both the specification, and the art support the position that GAGE is a melanoma-associated antigen.

Applicant states that all of the above-described references were properly incorporated by reference into the application at paragraph [0014] of Applicants' specification. Thus, Applicant argues that the proper support is found within the specification.

Response to Applicant's arguments

Applicant's arguments regarding the disclosure in prior arts WO 98/14464, Boel et al. (Immunity, vol. 2, pp. 167-175, pub. Feb. 1995), Van den Eynde, et al. (J. Exp. Med., I82:689-698 (1995)), and U.S. Pat. No. 6,013,765 supporting that a NY-ESO-1 antigen, a BAGE antigen, and a GAGE antigen are "melanoma-associated" tumor antigen, have been fully considered and found persuasive. Applicant clarifies on the record that a "melanoma-associated" tumor antigen

(a tumor-associated antigen, TAA) is not required to be "melanoma-specific" tumor antigen (a tumor-specific antigen, TSA)

It is noted that Applicant's arguments regarding incorporation of subject matter into this application by reference to WO 98/14464, Boel et al. (Immunity, vol. 2, pp. 167-175, pub. Feb. 1995; attached), and Van den Eynde, et al. (J. Exp. Med., I82:689-698 (1995), attached) and U.S. Pat. No. 6,013,765 is ineffective because the specification of instant application does not comply with 37 CFR 1.57(c). Further discussions regarding "incorporation by reference" are provided in maintained new matter rejection in this office action.

4. Claims 38 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed on 12/21/2009.*

Newly added claim 38 reads as follows: The method of claim 1 wherein the host shows no evidence of disease progression following step (b).

Newly added claim 39 reads as follows: The method of claim 1 wherein the host shows no radiological evidence of the metastases following step (b).

Claim 38 is unclear in scope because claim 1 recites "treating melanoma" whereas claim 38 recites "disease progression" which is broader in scope than the specified disease "melanoma" recited in claim 1.

Claim 39 is unclear because claim 39 recites the limitation "*the* metastases" in "radiological evidence of the metastases". There is insufficient antecedent basis for this limitation in the claim.

It is noted that the limitation "a host" recited in claim 1 reads on a mammal (i.e. *in vivo*) with melanoma as well as an *in vitro* tissue comprising melanoma. It is further noted that claim 1 does not recite any evidence of disease progression before step (b) or recites any radiological evidence of metastases before step (b).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

5. Claims 11 and 12 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Applicant's arguments filed on 12/21/2009 have been fully considered and found not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 6-7 of the office action mailed on 06/19/2009.

For the clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 6-7 of the office action mailed on 06/19/2009 is reiterated below.

Claim 11 recites "wherein the melanoma-associated tumor antigen is selected from the group consisting of gp100, MART-I/Melan A, gp75/TRP-I, tyrosinase, NY-ESO-I, melanoma

proteoglycan, a MAGE antigen, a BAGE antigen, a GAGE antigen, a fragments thereof, and a derivative thereof".

Claim 12 recites "wherein the melanoma-associated tumor antigen is selected from the group consisting of gpl00, MAGE-I, MAGE-2, MAGE-3, MAGE-4, MAGE-6, MAGEI2, MAGE-51, GAGE-1, and GAGE-2".

No support can be found in the specification that a NY-ESO-1 antigen, a BAGE antigen, a GAGE antigen recited in amended claim 11 and 12 are melanoma-associated tumor antigens. The status of art indicates that a NY-ESO-1 antigen, a BAGE antigen, and a GAGE antigen are not tumor specific antigens, and they are expressed in normal testis and placenta tissue. Accordingly, there is no evidence in the specification or in the art supports that a NY-ESO-1 antigen, a BAGE antigen, and a GAGE antigen are "melanoma-associated antigen" as recited in claims 11 and 12.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure" (emphasis added).

Applicant's arguments

Applicant states that as described in the preceding section, all of NY-ESO-1 antigen, BAGE antigen, and GAGE antigen are described in the specification and the art. All of the cited references were properly incorporated by reference into the application at paragraph [0014] of Applicants' specification. Thus, Applicants argues that the proper support is found within the Specification.. And, as described above, the art supports Applicants' position that the NY-ESO-1: BAGE, and GAGE are in fact understood to be melanoma-associated antigens. Applicant therefore argues that these rejections should be withdrawn.

Response to Applicant's arguments

The attempt to incorporate subject matter into this application by reference to WO 98/14464, Boel et al. (Immunity, vol. 2, pp. 167-175, pub. Feb. 1995; attached), and Van den Eynde, et al. (J. Exp. Med., I82:689-698 (1995), attached) and U.S. Pat. No. 6,013,765 is ineffective because the specification of instant application does not comply with 37 CFR 1.57(c).

MPEP 37 CFR 1.57(c)

"Essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. "Essential material" is material that is necessary to:

(1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of **35 U.S.C. 112**;

(2) Describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by the second paragraph of **35 U.S.C. 112**; or

(3) Describe the structure, material, or acts that correspond to a claimed means or step for performing a specified function as required by the sixth paragraph of **35 U.S.C. 112**.

In this instance, the specification filed on 10/22/2002 [US 2004/0223949, publication date 11/11/2004] provides the following statements:

[0014] The present invention provides reagents and methodologies useful for treating and/or preventing cancer. All references cited within this application are incorporated by reference.

[0018] TAs are typically classified into five categories according to their expression pattern, function, or genetic origin: cancer-testis (CT) antigens (i.e., MAGE, NY-ESO-1); melanocyte differentiation antigens (i.e., Melan A/MART-1, tyrosinase, gp100) ------ NY-ESO-1 (WO 98/14464; WO 99/18206) --- BAGE family antigens (Boel et al., Immunity, 2:167-175 (1995)), GAGE family antigens (i.e., GAGE-1,2; Van den Eynde et al., J. Exp. Med., 182:689-698 (1995); U.S. Pat. No., 6,013,765).

It is noted that the melanoma-associated antigens are essential materials of claimed methods, and WO 99/18206, Boel et al., Immunity, 2:167-175 (1995), and Van den Eynde et al., J. Exp. Med., 182:689-698 (1995) are not a U.S. patent or U.S. patent application publication required by MPEP 37 CFR 1.57(c). With regard to US patent No. 6,013,765, Applicant fails to provide any specific disclosure in the 6,013,765 patent that supports "a NY-ESO-1 antigen", "a BAGE antigen", and "a GAGE antigen" recited in amended claim 11 and 12 are melanoma-associated antigens.

The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(c). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

Claim Rejection – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Previous rejection of claims 1, 4-7, 11, 12, 14, 15, 18-22, 28-30, and 32-34 under 35 U.S.C. 103(a) as being unpatentable over **Paoletti** (U.S. patent number 5,942,235; issued on August 24, 1999; this reference has been cited in the office action mailed on 07/25/2006) in view of **Kirkwood et al.** (Kirkwood et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol.* 19(9): 2370-80, 2001; this reference has been cited in the office action mailed on 07/25/2006), and **Aarts et al.** (Aarts et al., Vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity, *Cancer Res.* 62(20):5770-7, 2002), is ***withdrawn*** because claim 1 has been amended.

Amended claim 1 filed on 12/21/2009 reads as follows: A method for treating melanoma comprising: (a) administering to a host a composition comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent such that the host

develops an immune response against the tumor antigen; and, (b) subsequently administering at least 10 M U/m2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the host; whereby the combination of steps a) and b) provides an enhanced T cell response in the host relative to that which occurs following step a) alone.

None of Paoletti , Kirkwood et al., and Aarts et al. explicitly discloses the limitation "as the sole active pharmaceutical agent" in the context of treating melanoma with melanoma-associated tumor antigen and IFN-α2b.

7. Previous rejection of claim 1, 11-13 and 24-26 under 35 U.S.C. 103(a) as being unpatentable over **Paoletti** (U.S. patent number 5,942,235; issued on August 24, 1999; this reference has been cited in the office action mailed on 07/25/2006) in view of **Kirkwood et al.** (Kirkwood et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol.* 19(9): 2370-80, 2001; this reference has been cited in the office action mailed on 07/25/2006), and **Aarts et al.** (Aarts et al., Vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity, *Cancer Res.* 62(20):5770-7, 2002), as applied to claims 1, 4-7, 11, 12, 14, 15, 18-22, 28-30, and 32-34 above, and further in view of **Kawakami et al.** (Kawakami et al., US Patent No. 5,844,075, issued on 12/01/1998), is ***withdrawn*** because claim 1 has been amended.

Amended claim 1 filed on 12/21 2009 reads as follows: A method for treating melanoma comprising: (a) administering to a host a composition comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent such that the host develops an immune response against the tumor antigen; and, (b) subsequently administering at least 10 M U/m2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the host; whereby the combination of steps a) and b) provides an enhanced T cell response in the host relative to that which occurs following step a) alone.

None of Paoletti , Kirkwood et al., Aarts et al., and Kawakami et al. explicitly discloses the limitation "as the sole active pharmaceutical agent" in the context of treating melanoma with melanoma-associated tumor antigen and IFN-α2b.

The following 103 rejections are necessitated by claim amendments filed on 12/21/2009. It is noted that Emtage et al. (US 2003/0113919, publication date 06/19/2003) has been cited to address the amendments "as the sole active pharmaceutical agent" recited in amended claim 1 and newly added claim 36. Newly added claims 35-39 filed on 12/21/2009 are included in the following 103 rejections.

8. Claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Paoletti** (U.S. patent number 5,942,235; issued on August 24, 1999; this reference has been cited in the office action mailed on 07/25/2006) in view of **Emtage et al.** (US 2003/0113919, publication date 06/19/2003, filed on 08/15/2002, provisional applications 60313438, 60313572, 60313573, 60313574 filed on 08/17/2001; this publication has been cited as reference A64 in the IDS filed by Applicant on 03/22/2010), **Kirkwood et al.** (Kirkwood et

al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol.* 19(9): 2370-80, 2001; this reference has been cited in the office action mailed on 07/25/2006), and **Aarts et al.** (Aarts et al., Vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity, *Cancer Res.* 62(20):5770-7, 2002).

Amended claim 1 filed on 12/21/2009 reads as follows: A method for treating melanoma comprising: (a) administering to a host a composition comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent such that the host develops an immune response against the tumor antigen; and, (b) subsequently administering at least 10 M U/m2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the host; whereby the combination of steps a) and b) provides an enhanced T cell response in the host relative to that which occurs following step a) alone.

Claim interpretation: The limitation "a host" reads on a mammal (i.e. *in vivo*) with melanoma as well as an *in vitro* tissue comprising melanoma. The limitation "wherein the host shows no evidence of disease progression following step (b)" recited in new claim 38 and "wherein the host shows no radiological evidence of the metastases following step (b)" are the consequences following the active steps. The consequences following the active steps are not active steps required for the claimed methods. In this regard, it is further noted that claim 1 does not recite any evidence of disease progression before step (b) or recites any radiological evidence of metastases before step (b).

Paoletti teaches attenuated recombinant viruses containing DNA coding for a cytokine and/or a tumor associated antigen, as well as methods and compositions employing the

viruses. Paoletti teaches that the recombinant viruses can be NYVAC or ALVAC recombinant viruses. The DNA can code for at least one of: human melanoma-associated antigen (MAGE-1; MZE-2) ; IL-2; IFNγ; IL-4; GMCSF; IL-12; B7; erb-B-2, and carcinoembryonic antigen (CEA). Paoletti teaches that the recombinant viruses and gene products are useful for cancer therapy (See abstract, and lines 40-45, column 13, Paroletti). Paoletti teaches that immune responses in a mammalian host against tumor cells are mediated by T-cells, particularly cytotoxic T lymphocytes (CTLs); white blood cells capable of killing tumor cells and virus-infected cells (column 7, lines 55-57). Furthermore, Paoletti teaches the administration of a cytokine secreted from modified tumor cells can subsequently be utilized for active immunization. The therapeutic potential for such an administration is based on the ability of cytokines to alter the presentation of TAAs to achieve systematic anti-tumor activity (See column 16, lines 3-8). Paoletti teaches that the vaccines or compositions can be co-administered or *sequentially* administered with other anti-neoplastic, anti-tumor or anti-cancer agents and/or with agents which reduce or alleviate ill effects of antineoplastic, anti-tumor or anti-cancer agents; again taking into consideration such factors as the age, sex, weight, and condition of the particular patient, and, the route of administration (See line 55-616, column 13, Paroletti)

Paoletti also teaches (1) viral vectors including poxvirus, vaccinia virus, and avipox virus (See, for instances, column 2, background of the invention, second paragraph; claims 1-8); NYVAC, ALVAC, and TROVAC based recombinant viruses expressing TAAs plus or minus specific cytokines for adoptive immunotherapy (See column 15, lines 45-48, column 17, lines 8-9); as well as canarypox virus (column 16, line 55) and fowlpox virus (column 16, line 64); (2) expression of tumor antigens --- CEA, carcinoembryonic antigen, (columns 70-77, example 17);

p53 (columns 65-68, example 15); MAGE-1 (columns 68-70, example 16); and cytokines --- human INFγ (columns 83-84, example 21), IL-2 (column 79-80, example 19) in both ALVAC-based viral vectors (which encompasses ALVAC or ALVAC(2) recited in claim 29-34 of instant application), and NYVAC based viral vectors.

Paoletti does not explicitly teach **(i)** a melanoma-associated tumor antigen or INF-α2b as the sole active pharmaceutical agent recited in amended claim 1, and gp100 peptides recited in newly added claim 36 as the sole active pharmaceutical agent, and **(ii)** subsequently administering at least 10 MU/m^2/day INF-α2b recited in step (b) of claim 1 for cancer vaccine regimen.

(i) Ematge et al. teaches peptides, including tumor-associated antigen gp100, and nucleic acid sequences encoding such peptides for use in diagnosing, treating, or preventing melanoma (See abstract, and paragraph [0010], Ematge et al. 2003). Ematge et al. teaches the following statements: "While the compositions of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other compositions or agents (i.e., other immunogenic targets, co-stimulatory molecules, adjuvants). When administered as a combination, the individual components can be formulated as separate compositions administered at the same time or different times, or the components can be combined as a single composition (See paragraph [0094] by Ematge et al. 2003, which is verbatim of [0074] of 2004/0223949, publication of instant application). Ematge et al. teaches a kit comprising a composition of the present invention is also provided. The kit can include a separate container containing a suitable carrier, diluent or excipient. The kit can also include an additional anti-cancer, anti-tumor or antineoplastic agent and/or an agent that reduces or

alleviates ill effects of antineoplastic, anti-tumor or anti-cancer agents for co- or sequential-administration. Additionally, the kit can include instructions for mixing or combining ingredients and/or administration (See paragraph [0100], Ematge et al. 2003).

(ii) With regard to administering at least 10 MU/m^2/day INF-α2b recited in step (b) of claim 1, and various vaccination of 10 MU/m2/day INF-α2b recited in claims 18-22, 28, and 29, **Kirkwood et al.** teach high dose INF-α2b, as the sole active pharmaceutical agent administered intravenously, in the treatment of patients with melanoma. Specifically, Kirkwood et al. teach high dose of INF-α2b (20 megaunits [MU]/m^2/d IV (intravenously) X 5 days a week for four week and 10 MU/m^2 SC (subcutaneously) three times per week [TIW] X 48 weeks), which was approved as adjuvant therapy for high-risk melanoma by the United States Food and Drug Administration (FDA) in 1995 (See first paragraph of Introduction, Kirkwood et al., 2001). The treatment significantly prolongs relapse-free survival and overall survival in high-risk melanoma patient. Kirkwood et al. teaches that dose reduction in the INF-α2b was performed in accordance with the common toxicity criteria established by the National Cancer Institute Treatment Evaluation Program. If criteria dictating dose modification were met, then treatment was withheld until recovery from toxicity. Treatment Statistical Analysis was resumed with a 33% dose reduction after the first treatment interruption for toxicity; a 66% dose reduction (i.e. at least 6 MU/m2/day INF-α2b as recited in claim 29 of instant application) was required after a Efficacy comparisons between the GMK and IFNu2b arms were second treatment interruption for toxicity (See bridging paragraph, page 2371-2372, Kirkwood et al., 2001). However, Kirkwood et al. do not teach combining high dose INF-α2b cytokine therapy with expression of a tumor antigen as a potent treatment of cancers.

With regard to subsequent administering a cytokine recited in step (b) of claim 1, **Aarts et al.** teaches vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity (See title and abstract, Aarts et al., 2002). Aarts et al. teaches various vaccination regimen starting with prime (i.e. initial) administration of a composition comprising a nucleic acid encoding human tumor antigen, carcinoembryonic antigen (CEA), expressed from a recombinant vaccinia (rV) vector such that the host develops an immune response against human CEA, followed by multiple subsequent booster vaccinations, which comprise administration of recombinant cytokines including recombinant GM-CSF and IL-2 (See Materials and Methods, and Table 1, Aarts, et al., 2002).

With regard to absence of repeating step (a) after step (b) recited in claim 35 and step (b) occurs between 15 and 17 months after step (a) recited in claim 37, these limitations are optimization of vaccination and obvious variants of the vaccination regimens taught by combined teachings of Aarts et al. (See materials and methods, pages 5771-5772, Aarts et al.) and Kirkwood et al. (See patients and methods, pages 2371-2372, Kirkwood et al.). In this regard, Applicant's attention is directed to the statements provided in MPEP § 2131.03.

2144.05 [R-5] Obviousness of Ranges
See MPEP § 2131.03 for case law pertaining to rejections based on the anticipation of ranges under 35 U.S.C. 102 and 35 U.S.C. 102/103.

II. OPTIMIZATION OF RANGES
A. Optimization Within Prior Art Conditions or Through Routine Experimentation
Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are

disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

B. Only Result-Effective Variables Can Be Optimized

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.). See also In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention to substitute the cytokine (including INFγ and IL-2) taught by combined teachings of Paoletti, Ematge et al., and Aarts et al. regarding treating melanoma by administering nucleic acid expressing a melanoma-associated antigen gp100, and subsequently administering a high dose INF-α2b taught by Kirkwood et al., and to follow the cancer vaccination treatment regimens taught by Aarts et al. and Kirkwood et al. to arrive at the claimed inventions of a method of treating melanoma as recited in claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37-39 of instant application.

One having ordinary skill in the art would have been motivated to substitute the cytokine (including INFγ and IL-2) taught by Paoletti, Emtage et al., and Aarts et al. in treating melanoma with a high dose INF-α2b taught by Kirkwood et al., and to follow the cancer vaccination treatment regimens taught by Aarts et al. and Kirkwood et al. because (i) Aarts et al. clearly provides a "proof of concept" that potent vaccines and vaccine strategies in combination with cytokines, may be essential to obtain the level of T-cell responses directed against a self-antigen that is necessary to achieve anti-tumor responses (See abstract, Aarts et al., 2002), and (ii) Emtage et al specifically teaches peptides, including tumor-associated antigen gp100, and nucleic acid sequences encoding such peptides for use in diagnosing, treating, or preventing melanoma, and the compositions can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other compositions or agents (i.e., other immunogenic targets, co-stimulatory molecules, adjuvants).

There would have been a reasonable expectation of success given (i) combinatory cancer therapy with expression of a melanoma-associated tumor antigen and expression of a cytokine

(including INFγ) either co-administered or sequentially administered, by the teachings of Paoletti, (ii) identification of multiple melanoma-associated antigen and expression of nucleic acid encoding the antigens in treating melanoma, by the teachings of Emtage et al. (Examples 1-4), (iii) the results of high dose of INF-α2b in the treatment of melanoma by the teachings of Kirkwood et al to achieve a tumor antigen specific immune response involving enhanced T cell response, and (iv) vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity in various treatment regimens, by the teachings of Aarts.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

9. Claims 24-26 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Paoletti** (U.S. patent number 5,942,235; issued on August 24, 1999; this reference has been cited in the office action mailed on 07/25/2006) in view of **Emtage et al.** (US 2003/0113919, publication date 06/19/2003, filed on 08/15/2002, provisional applications 60313438, 60313572, 60313573, 60313574 filed on 08/17/2001; this publication has been cited as reference A64 in the IDS filed by Applicant on 03/22/2010), **Kirkwood et al.** (Kirkwood et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol.* 19(9): 2370-80, 2001; this reference has been cited in the office action mailed on 07/25/2006), and **Aarts et al.** (Aarts et al., Vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity, *Cancer Res.* 62(20):5770-7, 2002), as applied to claims 1, 4-7,

11-15, 18-22, 28-30, 32-35 and 37-39 above, and further in view of **Kawakami et al.** (Kawakami et al., US Patent No. 5,844,075, issued on 12/01/1998).

The teachings of Paoletti, Emtage et al., Aarts et al., and Kirkwood et al. have been discussed in the preceding section of the rejection of claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37-39 under 35 U.S.C. 103(a) as being unpatentable over Paoletti in view of Kirkwood et al. and Aarts et al. It is noted the limitations recited in new claim 36 are obvious variant of the teachings by Aarts et al. regarding various subsequent booster vaccinations with a melanoma-associated tumor antigen, which includes gp100 taught by Emtage et al., and/or a cytokine.

None of Paoletti, Emtage et al., Kirkwood et al. and Aarts et al. teaches SEQ ID No:2 and SEQ ID No:3 of gp100 recited in claims 24-26 and 36.

However, at the time of filing of instant application, the gp100 as a melanoma-associated tumor antigen recited in claims 11-13 and 23, and SEQ ID No:2 and SEQ ID No:3 of gp100 recited in claims 24-26, were known in the art. For instant, **Kawakami et al.** teaches immunogenic peptides derived from melanoma antigen designated gp100, including SEQ ID No: 2 and SEQ ID No: 3 recited in claims 24-26 and 36 of instant application (See below for the alignment of SEQ ID No: 2 of instant application with SEQ ID No: 84 of Kawakami et al., and the alignment of SEQ ID No: 3 of instant application with SEQ ID No: 104 of Kawakami et al.).

SEQ ID No: 2

```
RESULT 1
US-08-417-174-84
; Sequence 84, Application US/08417174
; Patent No. 5844075
;  GENERAL INFORMATION:
;     APPLICANT:  KAWAKAMI, YUTAKA; ROSENBERG,
;     APPLICANT:  STEVEN A.
;     TITLE OF INVENTION:  MELANOMA ANTIGENS AND
;     TITLE OF INVENTION:  THEIR USE IN DIAGNOSTIC AND THERAPEUTIC
;     TITLE OF INVENTION:  METHODS
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;    NUMBER OF SEQUENCES:  126
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  MORGAN & FINNEGAN, L.L.P.
;      STREET:  345 PARK AVENUE
;      CITY:  NEW YORK
;      STATE:  NEW YORK
;      COUNTRY:  USA
;      ZIP:  10154
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  FLOPPY DISK
;      COMPUTER:  IBM PC COMPATIBLE
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  ASCII
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/417,174
;      FILING DATE:  05-APR-1995
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/231,565
;      FILING DATE:  22-APR-1994
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  CAROL M. GRUPPI
;      REGISTRATION NUMBER:  37,341
;      REFERENCE/DOCKET NUMBER:  2026-4124US1
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (212) 758-4800
;      TELEFAX:  (212) 751-6849
;      TELEX:  421792
;  INFORMATION FOR SEQ ID NO:  84:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  9
;      TYPE:  amino acid
;      STRANDEDNESS:  Unknown
;      TOPOLOGY:  Unknown
;    MOLECULE TYPE:  Peptide
US-08-417-174-84

  Query Match           100.0%;  Score 45;  DB 1;  Length 9;
  Best Local Similarity  100.0%;  Pred. No. 1e+06;
  Matches    9;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 IMDQVPFSV 9
              |||||||||
Db          1 IMDQVPFSV 9
```

SEQ ID No:3

```
RESULT 1
US-08-417-174-104
; Sequence 104, Application US/08417174
; Patent No. 5844075
;  GENERAL INFORMATION:
;    APPLICANT:  KAWAKAMI, YUTAKA; ROSENBERG,
;    APPLICANT:  STEVEN A.
;    TITLE OF INVENTION:  MELANOMA ANTIGENS AND
;    TITLE OF INVENTION:  THEIR USE IN DIAGNOSTIC AND THERAPEUTIC
;    TITLE OF INVENTION:  METHODS
;    NUMBER OF SEQUENCES:  126
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  MORGAN & FINNEGAN, L.L.P.
;      STREET:  345 PARK AVENUE
;      CITY:  NEW YORK
;      STATE:  NEW YORK
;      COUNTRY:  USA
```

```
;      ZIP:  10154
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  FLOPPY DISK
;      COMPUTER:  IBM PC COMPATIBLE
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  ASCII
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/417,174
;      FILING DATE:  05-APR-1995
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/231,565
;      FILING DATE:  22-APR-1994
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  CAROL M. GRUPPI
;      REGISTRATION NUMBER:  37,341
;      REFERENCE/DOCKET NUMBER:  2026-4124US1
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (212) 758-4800
;      TELEFAX:  (212) 751-6849
;      TELEX:  421792
;  INFORMATION FOR SEQ ID NO:  104:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  9
;      TYPE:  amino acid
;      STRANDEDNESS:  Unknown
;      TOPOLOGY:  Unknown
;    MOLECULE TYPE:  Peptide
US-08-417-174-104

  Query Match             100.0%;  Score 49;  DB 1;  Length 9;
  Best Local Similarity   100.0%;  Pred. No. 1e+06;
  Matches    9;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 YLEPGPVTV 9
              |||||||||
Db          1 YLEPGPVTV 9
```

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Kawakami et al. regarding the DNA encoding immunogenic peptides derived from melanoma antigen gp100, including SEQ ID No: 2 and SEQ ID No:3 recited in claims 24-26 and 36 of instant application, into the combined teachings of Paoletti, Emtage et al., Kirkwood et al., and Aarts et al. directing to a method for treating melanoma comprising : (a) administering to a host a comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent such that the host develops an immune response against the melanoma-associated tumor antigen; and (b) subsequently administering at least 10 MU/m^2/day INF-α2b as the sole active pharmaceutical

agent to the host, whereby the combination of step (a) and (b) provides an enhanced T cell response in the host relative to that which occurs of following step (a), to arrive at the claimed inventions as recited in claims 24-26 and 36.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Kawakami et al. on the DNA encoding DNA encoding immunogenic peptides derived from melanoma antigen gp100, including SEQ ID No: 2 and SEQ ID No: 3, into the combined teachings of Paoletti, Emtage et al., Kirkwood et al., and Aarts et al. because Kawakami et al. teaches that gp100 is a well-established melanoma tumor antigen and SEQ ID No: 2 and SEQ ID No: 3 are immunogenic to induce anti-melanoma T cells mediated immune response.

There would have been a reasonable expectation of success given (i) combinatory cancer therapy with expression of a tumor antigen and expression of a cytokine (including INFγ) either co-administered or sequentially administered, by the teachings of Paoletti, (ii) identification of multiple melanoma-associated antigen and expression of nucleic acid encoding the antigens in treating melanoma, by the teachings of Emtage et al. (Examples 1-4), (iii) the results of high dose of INF-α2b in the treatment of melanoma by the teachings of Kirkwood et al to achieve a tumor antigen specific immune response involving enhanced T cell response, (iv) vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity in various treatment regimens, by the teachings of Aarts, and (v) generation of cytotoxic T lymphocytes (CTL) immune response by administering nucleic acid encoding gp100, by the teachings of Kawakami et al. (See Example 3)

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and ***Response to Applicant's arguments***

Applicant's remarks regarding the previous rejection of record are addressed as the related to the new grounds of rejection set forth above. It is noted that **(i)** previous rejection of claims 1, 4-7, 11, 12, 14, 15, 18-22, 28-30, and 32-34 under 35 U.S.C. 103(a) as being unpatentable over Paoletti in view of Kirkwood et al. and Aarts et al. has been *withdrawn*, and **(ii)** previous rejection of claim 1, 11-13 and 24-26 under 35 U.S.C. 103(a) as being unpatentable over Paoletti in view of Kirkwood et al. and Aarts et al. as applied to claims 1, 4-7, 11, 12, 14, 15, 18-22, 28-30, and 32-34 above, and further in view of Kawakami et al. has been *withdrawn.*

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Paoletti, **Emtage et al.,** Kirkwood et al., and Aarts et al. (and Kawakami et al. for rejection of claims 24-26 and 36) have been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

10. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632